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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/087,441	PALSSON ET AL.	
	Examiner	Art Unit	
	Russell S. Negin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-74* is/are pending in the application.

4a) Of the above claim(s) *67-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,18-66 and 70-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Comments

Applicant's amendments and request for reconsideration in the communication filed on 31 January 2011 are acknowledged and the amendments are entered.

Claims 67-69 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7 June 2004.

Claims 1-16, and 18-74 are pending in the instant application.

Claims 1-16, 18-66, and 70-74 are examined in this Office action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following rejection is reiterated:

35 U.S.C. 103 Rejection #1:

Claims 1-12, 14-15, 18-28, 30, 32-46, 48-49, 51-63, and 70-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzimanikatis et al. [AIChE Journal, 1996, volume 42, pages 1277-1292] in view of Varma et al. [Bio/Technology. Volume 12, 1994, pages 994-998] in view of Grewal et al. [Protein Engineering, volume 7, 1994, pages 205-211].

Independent claims 1, 34, and 71 recite the same three core concepts: 1. providing of a data structure (comprising a stoichiometric matrix) containing a system of reactions where a subset of the reactions is regulated in an organism, 2. providing a constraint set under which the reactions are operated (of which a subset of the constraints are variable constraints), 3. optimizing an objective function using the stoichiometric matrix in order to determine a systemic property resulting from the system as a result of a flux distribution analysis; this system property is predictive of the biochemical reaction pathway in the organism. The claims use computers and the results are provided to a user.

Claims 1 and 34 have the extra limitation of a condition dependent constraint.

Claim 71 has the extra limitation of a condition dependent constraint and the further limitation of iteratively modifying the variable constraint.

The article of Hatzimanikatis et al. studies analysis and design of metabolic reaction networks via mixed integer linear optimization.

The first several sentences of the abstract of Hatzimanikatis et al. state:

> Improvements in bioprocess performance can be achieved by genetic modifications of metabolic control structures. A novel optimization problem helps quantitative understanding and rational metabolic engineering of metabolic reaction pathways.

Hatzimanikatis et al. continues in the abstract to describe that the problem to be solved is the systemic property of finding the optimal regulatory structure for maximization of phenylalanine selectivity in the microbial aromatic synthesis pathway; these systemic properties of determining fluxes and regulatory structures such as in Figure 1 of Hatzimanikatis et al. are predictive of how the biochemical reaction network functions in order to produce this maximization of phenylalanine selectivity in the microbial aromatic synthesis pathway.

An illustration of the reaction pathway studies on Hatzimanikatis et al. is shown in Figure 1 on page 1283 where several of the reactions are regulated (i.e. dotted lines in the Figure indicate regulatory reactions).

The system is mathematically described on page 1279 in Equation 1 and the paragraph bridging the first and second columns, which states:

> Consider a metabolic system consisting of n metabolites and m enzymatically-catalyzed reactions. We are in [sic] interested in studying how modifications of the expression levels and of the properties of the enzymes that catalyze these reactions affect metabolic functions of the system, such as metabolite concentrations, fluxes, and specific growth rate.

Consequently, flux distributions through this amino acid synthesis pathway are studied.

Constraints are described on pages 1282-1283 of Hatzimanikatis et al. The constraints include mass balances (non variable constraints), constraints based on continuous variables (variable constraints), and logical constraints based on the presence of certain regulatory loops (binary variable constraints). Some of the constraints (i.e. the binary constraints) are condition dependent on the presence of certain regulated reactions in the network. The values of the constraints are conditionally dependent on which of the eight pathways of solutions in Figure 2 on page 1284 of Hatzimanikatis et al. is selected.

The objective function is listed in Equation 12 on page 1281 of Hatzimanikatis et al. The goal of the study of Hatzimanikatis et al. is to maximize and minimize this function.

Table 1 on page 1285 of Hatzimanikatis et al. shows the solution for the continuous variables for six iterations in which variable functions and constraints are modified (i.e. optimized). Table 1 is also provides the results of the calculation to a user.

The "Computational Studies" starting on page 1283 of Hatzimanikatis et al. teaches that the pathways are applicably to bacterial organisms.

Hatzimanikatis et al. does not teach a data structure or database comprising reactions wherein the reactants and products are identified and are related or linked to a stoichiometric coefficient.

The article of Varma et al. studies metabolic flux balancing [title].

Specifically, equation 1 on page 994 and Figure 1 on page 995 of Varma et al. teach use of stoichiometric matrices to relate reactants to products in metabolic processes.

However, Hatzimanikatis et al. and Varma et al. do not describe the automated aspects of the instant set of claims.

The article of Grewal et al. studies computer modeling of the interactions between proteins involved in metabolism. Specifically, the last full paragraph in column 2 on page 205 of Grewal et al. describes use of the ALIGN program in the PIR software package run on a VAXII computer.

Claim 2 is further limiting in that said variable constraint is dependent upon the outcome of at least one reaction.

Claim 3 is further limiting in that said variable constraint is dependent upon the outcome of at least one regulatory event.

Claim 4 is further limiting in that the variable constraint is dependent on time.

Claims 5 and 38 are further limiting wherein said variable constraint is dependent upon the presence of a biochemical network participant.

Figure 2 on page 1284 of Hatzimanikatis et al. illustrates the eight best solution pathways for solving the optimization problem. Each of these solutions is interpreted to be calculated at a different time. Each pathway has a different set of reactions and regulatory events based on the calculation of different logical constraints (binary

variable constraint that indicate the existence or nonexistence of various regulatory loops- see bottom of second column of page 1282).

Claims 6 and 39 are further limiting wherein the participant is a substrate or product.

The reactions in Figure 1 of Hatzimanikatis et al. list substrates and products.

Claims 7 and 40 are further limiting wherein the said biochemical reaction network comprises metabolic reactions.

The pathway described in Figure 1 of Hatzimanikatis et al. is a metabolic pathway.

Claims 8 and 41 are further limiting comprising a regulatory data structure, wherein said variable constraint is dependent upon an outcome of a regulatory event represented by a data structure.

Logical constraints are binary variable constraints that indicate the existence or nonexistence of various regulatory loops- see bottom of second column of page 1282 of Hatzimanikatis et al.

Claims 9 and 42 are further limiting wherein one of the regulatory events can be inhibition or activation of a protein.

Hatzimanikatis et al. teaches activation and inhibition of metabolism in the third paragraph from the bottom in column 2 on page 1280 as examples of regulation events that affect the studied metabolic network.

Claims 10 and 43 are further limiting wherein the regulatory event is due to a signal transduction pathway.

The second paragraph of the Introduction of Grewal et al. on page 205 teaches the application of ligand-receptor interactions in signal transduction pathways.

Claims 11 and 44-45 are further limiting wherein said biochemical network and said regulatory data structure represent reactions or events that occur in a single cell.

The last line of page 1277 of Hatzimanikatis et al. indicates that the pathway occurs in a cell.

Claims 12 and 46 are further limiting wherein said biochemical reaction network represents reactions that occur in a first cell in a population of cells and said regulatory data structure events occur in a second cell.

The second paragraph of the Introduction of Grewal et al. on page 205 teaches the application of ligand-receptor interactions in signal transduction pathways. The first paragraph of the introduction suggests that signal transduction as a result of this study can occur extracellularly (i.e. between two cells).

Claims 14 and 48 are further limiting wherein there is a constraint function that correlates an outcome of a variable event with a variable constraint.

These functions are given on page 1283 of Hatzimanikatis et al. in Equations 22-26.

Claims 15 and 49 are further limiting wherein the constraint is binary.

The logical constraints of Hatzimanikatis et al. are binary constraints indicating the presence or absence of certain regulatory events in the synthesis pathway.

Claim 18 is further limiting comprising a range of feasible flux distributions.

Claims 19 and 53 are further limiting wherein the commands comprise an optimization problem. Claims 20 and 54 are further limiting wherein the optimization is linear or nonlinear optimization.

The objective of the study of Hatzimanikatis et al. is to use mixed-integer linear optimization to analyze a metabolic reaction (i.e. title). In doing so, flux distributions are calculated between reactions (i.e. see equation 1 on page 1279). Hatzimanikatis et al. teaches optimization, for example, in the title and conclusion of the study.

Claim 21 is further limiting that there is a user interface capable of sending at least one command for modifying said data structure. Claim 22 is further limiting wherein said user interface further comprises links which a user may select to access additional information relating to said plurality of reactions.

Figure 2 on page 1284 of Hatzimanikatis et al. illustrates such a user interface with visual links to each of the eight regulatory pathways. Each of the eight pathways is based on different optimization constraints resulting in different reaction networks.

Claims 23 and 56 are further limiting wherein said data structure comprises a set of linear algebraic equations.

Claims 24 and 57 are further limiting wherein said data comprises a matrix.

The equations of Hatzimanikatis et al. (i.e. equations 6-7 on page 1280 of Hatzimanikatis et al.) are examples of linear algebraic equations with relevant matrices.

Claims 25 and 58 are further limiting by demonstrating flux distributions as a flux distribution map.

Claim 26 is further limiting by annotating reactants and products.

Claim 27 is further limiting wherein a reactant is assigned a compartment.

Claim 28 is further limiting wherein a reactant is assigned to a compartment and another reactant is assigned to a different compartment.

Figure 1 of Hatzimanikatis et al. lists a flux distribution map with each member of the network being annotated with an abbreviation. Each member of the pathway is assigned to a different compartment within the Figure of Hatzimanikatis et al.

Claim 30 is further limiting wherein the annotation comprises a confidence limit for occurrence of the reaction.

Column 1 on page 1286 of Hatzimanikatis et al. demonstrates selecting a reaction scheme with 95 % selectivity by using three separate enzymes to conduct the reaction.

Claim 32 is further limiting wherein a specific listing of biochemical processes lists biosynthesis of an amino acid as a possible result of the network of reactions.

The objective of the pathways of Hatzimanikatis et al. is biosynthesis of the amino acid phenylalanine (see abstract).

Claim 33 is further limiting wherein there are a plurality of regulated reactions and variable constraints.

Figures 1-3 of Hatzimanikatis et al. illustrate a plurality of regulated reactions governed by a plurality of variable constraints.

Claim 35 is further limiting in that said variable constraint is dependent upon the outcome of at least one reaction.

Claim 36 is further limiting in that said variable constraint is dependent upon the outcome of at least one regulatory event.

Claim 37 is further limiting in that the variable constraint is dependent on time.

Figure 2 on page 1284 of Hatzimanikatis et al. illustrates the eight best solution pathways for solving the optimization problem. Each of these solutions is interpreted to be calculated at a different time. Each pathway has a different set of reactions and

regulatory events based on the calculation of different logical constraints (binary variable constraint that indicate the existence or nonexistence of various regulatory loops- see bottom of second column of page 1282).

Claim 51 is further limiting wherein said constraint function correlates a first set of outcomes of said regulatory data structure with a first binary value and a second set of outcomes of said regulatory data structure with a second binary value.

Claim 52 is further limiting wherein said constraint function correlates a set of outcomes of said regulatory data structure with a single integer value.

The logical constraints in the bottom of the second column of page 1282 of Hatzimanikatis et al. are binary variables indicating the presence of certain outcomes (i.e. presence) of certain regulatory reactions. Binary variables have single integer values.

Claim 55 is further limiting comprising a step of modifying said data structure or said constraint set, or both.

Claim 63 is further limiting wherein the constraint function is binary.

Figure 2 of Hatzimanikatis et al. illustrates eight modifications of the data structure. The presence of a regulatory reaction is based on the result of a binary constraint function indicating its existence.

Claim 59 is further limiting wherein a specific listing of biochemical processes lists biosynthesis of an amino acid as a possible result of the network of reactions.

The objective of the pathways of Hatzimanikatis et al. is biosynthesis of the amino acid phenylalanine (see abstract).

Claim 60 is further limiting wherein a systemic property is chosen from a given list including production of an amino acid.

The objective of the pathways of Hatzimanikatis et al. is biosynthesis of the amino acid phenylalanine (see abstract).

Claim 61 is further limiting wherein the systemic property comprises degradation.

The last full paragraph of column 2 on page 994 of Varma et al. describes that the mass balancing techniques are equally applicable to degradation as well as formation of metabolites.

Claim 62 is further limiting wherein there are a plurality of regulated reactions and variable constraints. Claim 63 is further limiting wherein the constraint function is binary.

Figures 1-3 of Hatzimanikatis et al. illustrate a plurality of regulated reactions governed by a plurality of variable constraints.

Figure 2 of Hatzimanikatis et al. illustrates eight modifications of the data structure. The presence of a regulatory reaction is based on the result of a binary constraint function indicating its existence.

Claim 70 is further limiting wherein a plurality of said reactions are regulated reactions and said constraints for said regulated reactions comprise boundary values.

Claim 72 is further limiting wherein said value is modified based on said flux distribution at said first time.

Claim 73 is further limiting wherein said value is modified based on a change in an environmental condition.

Claim 74 is further limiting wherein steps of claim 71 for a specified number of time points.

Equations 14 and 15 on page 1282 of Hatzimanikatis et al. illustrates boundary constraints intended to limit the pathway to physiological conditions. The pathways are consequently modified in such a way to function under physiological conditions. The multiple iterations in Table 1 of Hatzimanikatis et al. are interpreted to be conducted at multiple time points.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the flux distribution and reaction optimization of Hatzimanikatis et al. by use of the stoichiometric analyses of Varma et al. wherein the motivation would have been that the stoichiometric matrices of Varma et al. are necessary to provide an accurate mass balance over the metabolic system [see last full

paragraph of column 2 on page 994 of Varma et al.] It would have been further obvious to incorporate the multi-cellular signal transduction method of Grewal et al. in the method of Hatzimanikatis et al. and Varma et al. where the motivation would have been that the combination of better design of peptide-ligand interactions and signal transduction as in Grewal et al. is a step towards understanding biological results of this signal transduction such as steroid synthesis and secretion [see first paragraph of Discussion on page 210 of Grewal et al.] It would have been further obvious to computerize the methods using the VAXII hardware and software of Grewal et al. because the computer techniques of Grewal et al. lead to expedition and more powerful automation of the recited method steps [see column 2 on page 205 of Grewal et al.]

Response to Arguments:

Applicant's arguments filed 31 January 2011 have been fully considered but they are not persuasive. It is noted that some of the applicant's arguments are based on the "Response to Arguments" of the Office action of 8/2/10 rebutting the Remarks of 5/21/10.

Applicant first argues on pages 14-15 of the Remarks that page 15 of the Remarks of 5/21/10 does not contain an argument with regard to reasonable expectation of success; rather, applicant argues that page 15 of the Remarks of 5/21/10 merely sets up the analysis of pages 16-20 of the Remarks. This argument is not persuasive because lines 16-18 of the page 15 of the Remarks of 5/21/10 argues that

the references used in the above rejection "fail" to provide a reasonable expectation of success when combined.

Applicant next alludes to the evidence of Exhibit A (Burgard et al.) on pages 17-18 of the Remarks of 5/21/10 to argue (on page 15 of the instant Remarks) that the stoichiometric analysis of Hatzimanikatis et al. is not combinable or analogous with the flux balance analysis of Varma et al. Applicant argues that the stoichiometric analyses of Hatzimanikatis et al. reflect mass balances and not kinetics, and that flux balance analyses of Varma et al. reflect kinetic and not mass balances. This argument is not persuasive because first, the claim recite both flux balances to solve a mathematical optimization problem (i.e. step c of claim 1) in combination with stoichiometric matrices relating a plurality of reactants and products to chemical reactions (i.e. step a of claim 1). As a result, claim 1 is conducting both mass balances (step a) in combination with kinetics analyses that are based on the same stoichiometric matrices (step c). Consequently, if applicant's argument is valid Hatzimanikatis et al. is not combinable with Varma et al., then the embodiments of claim 1 are also not collectively functional.

Even assuming, *en arguendo*, that Hatzimanikatis et al. lacks flux balances and a reasonable expectation of success in combination with the flux balances of Varma et al., the "binary" stoichiometric matrices of Hatzimanikatis et al. (i.e. unity if a reaction occurs and zero if there is no reaction) is also a simple suggestion of the existence (or absence) of fluxes between the components of the biological network of Figure 1 on page 1283 of Hatzimanikatis et al. In addition, the flux balance analysis of Varma et al.

uses stoichiometric matrices to assist in flux balancing [equation 1 on page 994 of Varma et al. and Figure 1 on page 995 of Varma et al.].

Applicant next argues on page 16 of the Remarks that the "binary" stoichiometric matrix of Hatzimanikatis et al. is not consistent with the definition of "stoichiometric matrix" cited in paragraph 41 of the specification. Applicant quotes this paragraph on page 16 of the Remarks by stating:

> [A] numerical constant correlating the quantity of one or more reactants and one or more products in a chemical reaction . . . each with a discrete stoichiometric coefficient assigned to them to describe the chemical conversion taking place in the reaction.

First, paragraph 41 of the specification, as an entirely (without the ellipse) discloses:

> ***As used herein, the term "stoichiometric coefficient" is intended to mean*** a numerical constant correlating the quantity of one or more reactants and one or more products in a chemical reaction. ***The reactants in a data structure or more of the invention can be designated as either substrates or products of a particular reaction,*** each with a discrete stoichiometric coefficient assigned to then to describe the chemical conversion taking place in the reaction. ***Each reaction is also described as occurring in either a reversible or irreversible reaction. Reversible reactions can either be represented as one reaction that operates in both the forward and reverse direction, or decomposed into two irreversible reactions, one corresponding to the forward reaction and the other corresponding to the backward reaction.***

First, paragraph 41 requires that the reaction stoichiometric coefficients be discrete (zero and unity in the "binary" stoichiometric coefficient matrices of Hatzimanikatis et al. are discrete values). Second, Figure 1 of Hatzimanikatis et al. illustrates a network of reactants and products with the ultimate goal of producing aromatic amino acids. Third, just as paragraph 41 of the specification relates stoichiometric matrices to determine whether the reversibility of reactions, the presence (stoichiometric coefficient of unity) and absence (stoichiometric coefficient of zero) of

the potential "dotted line" pathways in Figure 1 of Hatzimanikatis et al. is reflected in the stoichiometric matrix governing the illustrates network of reactions.

Applicant next argues on page 16 of the Remarks that the amendments to the independent claims "employing flux balances" to solve optimization problems further distinguishes the claims from the prior art. This argument is not persuasive because Varma et al. teaches flux balance analysis using stoichiometric matrices, and Hatzimanikatis et al. suggests flux balance analysis to solve reaction network optimization (i.e. while a stoichiometric coefficient of unity between a reactant and a product indicates the presence of a flux, a stoichiometric coefficient of zero between a reactant and a product indicates the absence of a flux).

Applicant continues to argue on pages 16-17 of the Remarks that Hatzimanikatis et al. and Varma et al. are not combinable and analogous because the "binary stoichiometric matrix" of Hatzimanikatis et al. "arbitrarily" assigns coefficients of zero or unity based on whether the reaction occurs without quantifying the conversion of reactant to product. This argument is not persuasive because the coefficient for each component in the network of Figure 1 of Hatzimanikatis et al. is interpreted to be unity because there is no other integer used as a coefficient. Second, the complete network of Figure 1 of Hatzimanikatis et al. is modified to optimize three independent problems associated with optimizing amino acid selectivity with the best results (i.e. stoichiometric matrices) for each of the three problems in Figures 2, 3, and 4, respectively. Consequently, the existence or absence of reversible pathways in aromatic amino acid synthesis is chosen in a way to optimize a specific problem- and not arbitrarily.

Applicant next reiterates (on pages 17-18 of the Remarks) that the amendments to the independent claims distinguish the claims from the stoichiometric model of Hatzimanikatis et al. This argument is not persuasive because, as discussed above and reiterated here, Varma et al. teaches flux balance analysis using stoichiometric matrices, and Hatzimanikatis et al. suggests flux balance analysis to solve reaction network optimization (i.e. while a stoichiometric coefficient of unity between a reactant and a product indicates the presence of a flux, a stoichiometric coefficient of zero between a reactant and a product indicates the absence of a flux). In Hatzimanikatis et al., the presence or absence of reverse reactions to determine all possible fluxes in a reaction network is made possible by use of the binary stoichiometric matrices in Figures 2-4 of Hatzimanikatis et al. that solve three optimization problems, respectively.

Applicant next alludes to the evidence of Exhibit A (Burgard et al.) on pages 17-18 of the Remarks of 5/21/10 to argue (on page 18 of the instant Remarks) that the stoichiometric analysis of Hatzimanikatis et al. teaches undesirable and unnecessary information is not combinable or analogous with the flux balance analysis of Varma et al. This argument is not persuasive because unlike stoichiometric matrices that are limited to using positive numbers as coefficients, the stoichiometric matrices of Hatzimanikatis et al. incorporate the number "zero." Consequently, it is necessary (and desirable) to possess a value of unity and NOT zero as a starting point for modeling the kinetics and flux balance of a reaction. (If a stoichiometric coefficient for a particular reaction is zero, the reaction network yields data pertinent to the flux distribution of the

network in that it is known from the start that there is NO flux between the reactant and product of the particular reaction).

Applicant next argues that the "binary stoichiometric matrices" of Hatzimanikatis et al. are not equivalent to the stoichiometric matrices of Varma et al. This argument is not persuasive because both sets of stoichiometric matrices are within the definition of "stoichiometric matrix" in paragraph 41 of the specification.

The following rejection is reiterated:

35 U.S.C. 103 Rejection #2:

Claims 31 and 64-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzimanikatis et al. in view of Varma et al. in view of Grewal et al. as applied to claims 1-12, 14-15, 18-28, 30, 32-46, 48-49, 51-63, and 70-74 above, and further in view of Liao et al. [Biotechnology and Bioengineering, volume 52, 1996, pages 129-140].

Claim 31 is further limiting comprising a gene database relating one or more reactions in said data structure with one or more open reading frames or proteins in a particular organism.

Claim 64 is further limiting comprising a gene database relating one or more reactions in said data structure with one or more open reading frames or proteins in a particular organism.

Claim 65 is further limiting comprising identifying an open reading frame that encodes a protein that performs a plurality of reactions.

Claim 66 is further limiting comprising identifying a protein that performs a reaction in the plurality of reactions.

Hatzimanikatis et al., Varma et al., and Grewal et al. make obvious a method of using linear optimization to optimize a regulated reaction, as set forth above.

Hatzimanikatis et al., Varma et al., and Grewal et al. do not teach use of open reading frames and gene databases.

The article of Liao et al. investigates pathway analysis, engineering, and physiological considerations for redirecting central metabolism.

Figure 3 on page 132 of Liao et al. illustrates a data base of relevant expression from different mutant genes with open reading frames expressing the necessary and identified proteins listed perform the metabolic pathways of Liao et al. in order to produce glucose.

The sentences bridging columns 1 and 2 on page 137 of Liao et al. state:

> We have presented evidence suggesting that some of these metabolites serve as an internal signal in regulating glucose transport, heat shock response, and nitrogen regulation.

Consequently, the metabolites associated with the genes play a significant role in regulating biologically important responses.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the reaction optimization of Hatzimanikatis et al., Varma et al., and Grewal et al. by incorporating the genetic analyses of the metabolic pathways of glucose as taught by Liao et al. where the motivation would have been a better understanding of an internal method of regulating biological responses such as glucose

transport, heat shock response, and nitrogen regulation as taught by Liao et al. on page 137.

Response to Arguments:

Applicant's arguments filed 31 January 2011 have been fully considered but they are not persuasive.

Applicant argues on page 19 of the Remarks that the reference of Liao et al. does not overcome the alleged deficiencies of Hatzimanikatis et al., Varma et al., and Grewal et al. This argument is not persuasive because the combination of Hatzimanikatis et al., Varma et al., Grewal et al., and Liao et al. teaches all of the limitations of the instantly rejected claims.

The following rejection is reiterated:

35 U.S.C. 103 Rejection #3:

Claims 16 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzimanikatis et al. in view of Varma et al. in view of Grewal et al. as applied to claims 1-12, 14-15, 18-28, 30, 32-46, 48-49, 51-63, and 70-74 above, and further in view of Kim et al. [US 2002/00087275 A1; filed 31 July 2001].

Claims 16 and 50 are further limiting by incorporating Boolean operators into the reaction pathway.

Hatzimanikatis et al., Varma et al., and Grewal et al. make obvious a method of using linear optimization to optimize a regulated reaction, as set forth above.

Hatzimanikatis et al., Varma et al., and Grewal et al. do not teach usage of Boolean analysis in the reaction pathways.

The study of Kim et al. studies visualization and manipulation of biomolecular relationships using graph operators. Figure 1 of Kim et al. illustrates such a graph theory. Specifically, Paragraph [0097] describes use of Boolean variables when examining the reaction network.

This analysis of Kim et al. allows for computational algorithms for representing and analyzing large and heterogeneous molecular biological data (see paragraph [0002]). The last sentences of paragraph [0010] of Kim et al. explain a disadvantage of the prior art improved upon in Kim et al.

> However the computation of these [prior art] systems were carried out at the database level by querying a database for all potential consecutive binary gene pairs, and subsequently, integrating them into pathways.... More complex analyses such as comparing disparate data sets, exploring gene network structures, and inferring pathways and gene functions, are either beyond the capacity of these systems or computationally too expensive to perform.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the reaction optimization of Hatzimanikatis et al., Varma et al., and Grewal et al., by incorporating the genetic graphing algorithms taught by Kim et al. where the motivation would have been a better understanding of complex metabolic networks, as described in paragraphs [0002] and [0010] of Kim et al.

Response to Arguments:

Applicant's arguments filed 31 January 2011 have been fully considered but they are not persuasive.

Applicant argues on pages 19-20 of the Remarks that the reference of Kim et al. does not overcome the alleged deficiencies of Hatzimanikatis et al., Varma et al., and Grewal et al. This argument is not persuasive because the combination of Hatzimanikatis et al., Varma et al., Grewal et al., and Kim et al. teaches all of the limitations of the instantly rejected claims.

The following rejections are reiterated:

35 U.S.C. 103 Rejection #4:

Claims 13 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzimanikatis et al. in view of Varma et al. in view of Grewal et al. as applied to claims 1-12, 14-15, 18-28, 30, 32-46, 48-49, 51-63, and 70-74 above, and further in view of Vissing et al. [Neurology, 1996, volume 47, pages 766-771].

Claims 13 and 47 are further limiting in that the events occur in a multicellular organism.

Hatzimanikatis et al., Varma et al., and Grewal et al. make obvious an automated method of using linear optimization to optimize a regulated reaction, as set forth above.

Hatzimanikatis et al., Varma et al., and Grewal et al. do not teach regulated reaction networks in multicellular organisms.

The study of Vissing et al. examines the sources of enhanced glucose production during exercise in humans with blocked glycolysis caused by muscle phosphofructokinase deficiency.

The purpose of understanding this phenomenon is relevant for better understanding of diseases involving altered glucose production during glycolysis (i.e. McArdle's disease, as set forth in the paragraph bridging columns 1 and 2 on page 766).

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the reaction optimization of Hatzimanikatis et al., Varma et al. and Grewal et al., by incorporating the metabolic pathway of glycolysis in humans of Vissing et al. where the motivation would have been a better understanding of diseases affected by abnormal glycolysis in multicellular organisms, as taught on page 766 of Vissing et al.

Response to Arguments:

Applicant's arguments filed 31 January 2011 have been fully considered but they are not persuasive.

Applicant argues on page 20 of the Remarks that the reference of Vissing et al. does not overcome the alleged deficiencies of Hatzimanikatis et al., Varma et al., and Grewal et al. This argument is not persuasive because the combination of Hatzimanikatis et al., Varma et al., Grewal et al., and Vissing et al. teaches all of the limitations of the instantly rejected claims.

The following rejection is reiterated:

35 U.S.C. 103 Rejection #5:

Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzimanikatis et al. in view of Varma et al. in view of Grewal et al. as applied to claims 1-12, 14-15, 18-28, 30, 32-33, 34-46, 48-49, 51-63, and 70-74 above, and further in view of Callis [The Plant Cell, volume 7, 1995, pages 845-857].

Claim 29 is further limiting wherein annotation comprises assignment of an open reading frame to a corresponding protein.

Hatzimanikatis et al., Varma et al., and Grewal et al. make obvious a method of using linear optimization to optimize a regulated reaction, as set forth above.

Hatzimanikatis et al., Varma et al., and Grewal et al. do not teach metabolism of proteins.

The article of Callis studies the regulation of protein degradation. Specifically, the paragraph bridging columns 1 and 2 on page 850 demonstrates assignment of an open reading frame encoded by cDNA consistent with specific peptides.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the automated reaction optimization of Hatzimanikatis et al., Varma et al. and Grewal et al., by assigning open reading frames to specific proteins as taught by Callis, where the motivation would have been that such an assignment facilitates mapping between DNA and proteins [see paragraph bridging columns 1 and 2 on page 850 of Callis]. There would have been a reasonable expectation of success in combining the analysis of general and bacterial metabolism of Hatzimanikatis et al. with annotation comprising assigning open reading frames of the plant metabolism of Callis

because the assignment of open read frames to peptides is a robust concept, generally applicable to all organisms.

Response to Arguments:

Applicant's arguments filed 31 January 2011 have been fully considered but they are not persuasive.

Applicant argues on page 20 of the Remarks that the reference of Callis does not overcome the alleged deficiencies of Hatzimanikatis et al., Varma et al., and Grewal et al. This argument is not persuasive because the combination of Hatzimanikatis et al., Varma et al., Grewal et al., and Callis teaches all of the limitations of the instantly rejected claims.

Applicant additionally argues on page 20 of the Remarks that there is no teaching or suggestion of annotation of at least one reactant in a plurality of reactants or at least one reaction is a plurality of reactions by assignment to an open reading frame. The argument is not persuasive because Callis is only relied upon to demonstrate the annotation of proteins involved in metabolism with open reading frames (paragraph bridging columns 1 and 2 on page 850 of Callis); the remaining limitations of claim 29 (and claims dependent therefrom) are taught in Hatzimanikatis et al., Varma et al., and/or Grewal et al. As stated above and reiterated here, there would have been a reasonable expectation of success in combining the general and bacterial metabolism of Hatzimanikatis et al. with annotation comprising assigning open reading frames of the

plant metabolism of Callis because the assignment of open read frames to peptides is a robust concept, generally applicable to all organisms.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 8:30 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571) 272-0720.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Russell S. Negin/
Primary Examiner, Art Unit 1631
5 April 2011